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The fatty acid amine hydrolase inhibitor URB597: evaluation of its antidepressant profile

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The endocannabinoid system may be involved in the pathogenesis of depression by interacting with the serotonergic system. In preliminary studies, it has been reported that URB597 (a fatty acid amine hydrolase inhibitor) may exhibit antidepressant actions by increasing anandamide levels. The aim of this study was to evaluate if seven days administration of URB597 induces similar behavioural, neurochemical and functional adaptive changes to those induced by fluoxetine, using the animal model of depression of bilateral olfactory bulbectomy (OB) in mice.

The experiments were carried out in C57BL/6 mice (25±0.1 g). All *in vivo* experiments were conducted under standard housing conditions (21±0.1ºC). Olfactory bulbectomy was performed under isofluorane anaesthesia and the experiments performed four weeks after surgery. Animals were treated with 1% DMSO i.p. (control group), fluoxetine (160 mg/l p.o.) or URB597 (0.3 mg/kg i.p.) and the experiments were carried out 24 hours after the last administration. Statistical analysis of the results was made using One-way Anova or unpaired Student t-test where appropriate (level of significance $p< 0.05$).

First, behavioural testing was carried out in naïve mice in order to evaluate the possible antidepressant activity of URB597. Immobility time in the forced swimming test was decreased after URB597 administration (21.2±7.4% of reduction *vs* control, n=8 for both groups; $p<0.05$) although no changes were found in the anhedonic paradigm of sucrose intake. Regarding 5-HT_{1A} receptors, no changes were observed in 5-HT_{1A} receptor density, however, URB597, unlike fluoxetine, increased the efficacy of 8-OH-DPAT to stimulate [^{35}S]GTPγS binding in the CA3 (+15.2±5.7%, n=11 for both groups; $p<0.05$). Also, 8-OH-DPAT-induced hypothermia (-2.7±0.4ºC in saline-treated animals; n=8) was attenuated by URB597 (-1.5±0.3, n=8; $p< 0.01$), as observed with fluoxetine (-0.6 ±0.2, n=5; $p< 0.01$). On the other hand, both URB597 and fluoxetine decreased BDNF mRNA expression in the hippocampus.

Olfactory bulbectomy induced an anhedonic response, an increase in 5-HT_{1A} receptor density and an increase in BDNF mRNA expression in some cortical areas. Subchronic fluoxetine and URB597 were not able to modulate these behavioural and neurochemical changes induced by OB. However, URB597 reduced the efficacy of 8-OH-DPAT to stimulate [^{35}S]GTPγS binding in dorsal raphe nucleus (-14.2±3.8% *vs* OB-vehicle, n=5 for both groups; $p<0.05$) and a similar effect was observed with fluoxetine (-14.6±6,2%, n=5; $p<0.05$). Finally, 8-OH-DPAT-induced hypothermia was enhanced in OB mice (-3.2±0.3ºC, n=6 *vs* -2.3±0.2ºC, n=5 for OB-vehicle and sham respectively; $p< 0.01$). This 5-HT_{1A}-receptor hypersensitivity induced by OB was totally reversed following subchronic URB597 and fluoxetine.

In conclusion, URB597 exhibits a quite similar profile to the antidepressant fluoxetine in normal and OB mice. It has been described that olfactory bulbectomy is a validated model of depression in which neurochemical and behavioural changes are reversed by chronic administration of clinically effective antidepressants. Our findings demonstrate the existence of some neurochemical and functional changes after 7 days treatment with URB597, as observed with fluoxetine, which may be contributing to its antidepressant profile.

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